301

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Studies in Experimental Traumatic Shock

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BOSTON

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STUDIES IN EXPERIMENTAL TRAUMATIC SHOCK

V. THE CRITICAL LEVEL IN A FALLING BLOOD PRESSURE*

W. B. CANNON, M.D., AND McKEEN CATTELL, PH.D.
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Gesell has distinguished between the *initiating* and the *sustaining* factors in shock. The previous paper of this series [1] was concerned with evidence for a toxic agent developed in damaged tissue and acting as an initiating factor in the onset of shock. The present paper is concerned with a sustaining factor—low blood pressure.

The low blood pressure in both experimental and clinical shock is explained by a diminution of blood volume, an actual decrease in the amount of fluid which is kept circulating. In the early stages of secondary shock, however, the diminished volume may not be associated with a reduced arterial pressure. The only way in which the pressure can be maintained in the presence of a smaller amount of circulating fluid is by a lessening of the capacity of the circulatory system. This diminished capacity is the consequence of extra activity of the vasoconstrictor center causing greater contraction of peripheral vessels. When the blood pressure begins to fall, there may also be passive contraction of these vessels because they are no longer distended by the internal pressure which normally prevails. With further development of shock, there is a fall of arterial pressure below the limits of normal variation, a fall which is accounted for by reduction of the blood volume below the minimal capacity of the system and by a final relaxation of vascular tone as the vasomotor system becomes less active.

The effects of the changes above outlined are fundamentally important to an understanding of the sequence of events in shock. In order to comprehend their significance, it is necessary to refer to the principles of the circulation. We must keep in mind the fact that the blood circulates in order to supply with food and oxygen the tissues which are remote from the alimentary tract and the lungs, and to carry waste from the tissues to surfaces where it may be excreted. The interchange between the flowing stream and the active tissues occurs in the *capillary* portion of the circulatory system. This is the essential region. All other parts of the circulation—heart, arteries and veins—exist in order to provide a continuous flow of blood through the capil-

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* From the Laboratory of Physiology of the Harvard Medical School.

1. Cannon, W. B.: Studies in Experimental Traumatic Shock, Arch. Surg. **4**:1 (Jan.) 1921.

laries. The high head of pressure normally maintained in the arteries serves, first, to keep a constant flow passing through the capillaries in all parts of the body no matter what extra demands are placed on the general supply of blood by organs which, becoming active, have dilated vessels. Secondly, this high head of pressure assures speed in the passage of blood from the heart back to the heart again. And since the function of the blood as a common carrier depends on the number of trips which it makes from places where it is loaded to where it is unloaded, the speed of the circulation is evidently an important determinant of the capacity of the blood for service in the body.

THE EFFECTS OF DECREASED BLOOD VOLUME

With a decreased volume of blood, the blood pressure may still remain at its normal level because of compensatory vasoconstriction. One might suppose from the restored blood pressure that the blood supply to all parts of the organism is occurring at its normal rate. The admirable investigations of Gesell [2] have shown, however, that this is far from being the case. The vasoconstriction which takes place when, in consequence of hemorrhage or tissue injury, the blood volume is reduced, is not uniform throughout the vascular distribution. Gesell's observations prove that under such circumstances the volume-flow through the submaxillary gland, for example, is greatly diminished. In one instance, a removal of 10 per cent. of the estimated blood volume of the animal caused a reduction of the volume-flow per minute through this gland amounting to 60 per cent. of the basal flow (i.e., the amount passing through the gland when at rest). This occurred even though there was no fall of arterial pressure. The volume-flow is obviously of the utmost importance in the delivery of oxygen to the tissues, for each red blood corpuscle is a carrier. If the number of carriers is reduced to this great degree as a consequence of slight hemorrhage or slight reduction of blood volume, it is obvious that the tissues are in danger of an insufficient supply.

It should not be supposed that all parts of the body are affected in the same way as the submaxillary gland when vasoconstriction compensates for diminished volume. There is good evidence [3] that in the presence of normal arterial pressure the blood vessels of the central nervous system and the heart do not undergo contraction. The effect, therefore, of a peripheral constriction which would shut down the volume-flow in peripheral structures would serve to maintain an adequate volume-flow in the essential organs.

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2. Gesell, R.: Am. J. Physiol. **47**:502 (Jan.) 1919.

3. Wiggers, C. J.: Modern Aspects of the Circulation in Health and Disease, New York, Lea and Febiger, 1915, pp. 83, 84.

THE EFFECTS OF DECREASED ARTERIAL PRESSURE

Gesell's studies prove that the volume-flow to peripheral organs is more diminished by reduction of blood volume than by reduction of blood pressure. When blood pressure begins to fall, however, the force which is driving the blood through the capillaries begins to become less effective, consequently the rate of flow will, as a rule, steadily diminish as the pressure falls. Thus the volume-flow not only to peripheral structures but also to the essential organs, such as the central nervous system and the heart, becomes gradually less and less.

Diminished blood volume, therefore, results in a lessened blood supply to peripheral tissues because of a primary vasoconstriction: and lessened blood pressure results in diminished blood supply both to peripheral tissues and to central organs because of a slower flow. All parts of the body may then begin to suffer from disturbances of the circulation, initiated by diminished volume of blood and continued as the volume becomes less and less.

The materials delivered to the tissues by the flowing blood may be classified into food, water and oxygen. The degree of dependence of cells on these materials varies with the materials and also with different groups of cells. Thus there may be prolonged absence of fresh food supply in the blood without disturbance of function. A less prolonged absence of fresh water supply in the circulating stream is also endured without serious damage. The need for oxygen, however, is quite different from the need for either food or water. It is urgently necessary that oxygen be continuously delivered if tissues are to be kept active. It becomes a matter of importance, therefore, to inquire into the evidence that there actually is an insufficient oxygen supply delivered to the tissues when the flow of blood through the capillaries is much reduced.

RELATION OF REDUCED ALKALI RESERVE TO BLOOD PRESSURE

In 1910, Henderson[4] pointed out that in the absence of an adequate supply of oxygen the development of acid substances in the tissues might be expected, in consequence of the partial asphyxia. Later, Crile[5] and his co-workers reported results which indicated that a condition of "acidosis" is present in various clinical states, including shock. And in 1917, during a study of the toxemia of gas gangrene, Wright[6] observed a reduction of the alkalinity of the blood serum as determined by titration with acid to a certain end point. Patients suffering from gas gangrene have many of the symptoms of shock, and Wright argued

4. Henderson. Yandell: Am. J. Physiol. **27**:167, 174, 1910.

5. Crile, G. W.: The Origin and Nature of Emotions, Philadelphia, W. B. Saunders Company, 1915, p. 227.

6. Wright, A. E.: Lancet **1**:8 (Jan. 6) 1917.

that the "acidemia," as he called it, of this condition was the cause of these symptoms.

During the summer of 1917, at Béthune, one of us (W.B.C.) made use of the then newly described method and apparatus introduced by Van Slyke,[7] and obtained estimates of the sodium bicarbonate, or alkali reserve of the blood plasma in wounded men suffering from the low arterial pressure which accompanies shock, hemorrhage and gas gangrene.[8] The results given by the Van Slyke instrument are expressed in percentage by volume of carbon dioxid which can be separated from the plasma after it has been exposed to an atmosphere containing 5.5 per cent. of the gas (the concentration existing in the pulmonary alveoli and present in the final air of an extreme expiration). Any figures lower than 50 per cent. by volume of carbon dioxid in the plasma of adults indicates a reduction of the alkali reserve below the normal range of variation. In the sense defined by L. J. Henderson[9] and by Van Slyke and Cullen,[10] readings below this normal range may be regarded as marking a condition of "acidosis." The expressions "reduction of the alkali reserve" and "reduction of the carbon dioxid capacity" may be used interchangeably with the reduction of blood alkali. In the Béthune cases, observations were made on the relation of reduced alkali reserve to blood pressure, to pulse, and respiration, and to other attendant conditions.

In forty-five different coincident determinations of blood pressure and carbon dioxid capacity, a rough relation between the two was found; in general, the lower the blood pressure, the lower the alkali reserve. This relation is illustrated in Table 1.

TABLE 1.—Relation Between Blood Pressure and Carbon Dioxid Capacity

No. of Cases	Carbon Dioxid Capacity Percentage by Volume	Systolic Arterial Pressure in Millimeters of Mercury
6	50 to 59 (av. 53)	90
25	40 to 49 (av. 44)	75
8	30 to 39 (av. 35)	72
6	20 to 29 (av. 24)	59

It is noteworthy that in thirty-nine of the forty-five cases, the average systolic pressure was 75 millimeters of mercury, or less, and that in all these there was a carbon dioxid capacity of less than 50 per cent. by volume, i.e., below the normal range. Furthermore, as the average carbon dioxid capacity was low, the average systolic pressure

7. Van Slyke, D. D.: J. Biol. Chem. **30**:347 (June) 1917.

8. Cannon, W. B.: Acidosis in Shock, Hemorrhage and Gas Infection, J. A. M. A. **70**:531 (Feb. 23) 1918.

9. Henderson, L. J.: Science, **37**:389, 1913.

10. Van Slyke, D. D., and Cullen, G. E.: J. Biol. Chem. **30**:292 (June) 1917.

was likewise low. In the cases mentioned above, some process had been going on for hours, often six or eight, that had brought about the state observed on admission of the patient. The progressive character of the process was shown in one instance in which the carbon dioxid capacity one hour after the wounding was 50 per cent., and five hours later, with no corrective treatment, it had fallen to 40 per cent. The condition has a gradual rather than an acute onset.

EXPLANATION OF THE DIMINISHED ALKALI RESERVE

Two explanations have been offered to account for the reduction of the bicarbonate of blood plasma: one that nonrespirable acid, such as lactic acid, develops in the tissues because of oxygen want, and, uniting with the sodium of sodium bicarbonate, drives off carbon dioxid, which is breathed out; the other that excessive respiration diminishes the carbonic acid in the blood with consequent *alkalosis,* and that thereupon the extra alkali disappears into the tissues, or diffuses into body fluids outside the blood, or escapes through the kidneys. The former process has been designated by Henderson as the "acidotic," the latter as the "acapnial" reduction of blood alkali.

There is a good deal of evidence that an insufficient oxygen supply to the tissues results in formation of lactic acid. Zillesson,[11] 1891, noted that when the blood supply of the muscles or liver was limited, lactic acid was formed in these organs. Araki[12] proved that lactic acid (lactates) were present in the urine of dogs and rabbits in conditions of oxygen lack brought about by breathing carbon monoxid or by a low percentage of oxygen in the inspired air. In an artificially produced anemia, Irisawa[13] found that the lactic acid content of the blood increased as the oxygen lack became more severe. More recently, Milroy[14] and Penfield[15] have reported that reduction of blood alkali appears typically after a severe hemorrhage. And within the last few years, a number of workers have published papers on experimental shock in which there is agreement that a decreasing alkali reserve is associated with a falling blood pressure (McEllroy,[16] Guthrie,[17] Erlanger and Gasser[18] and Gesell[19]). The low blood pressure in the late stages

11. Zillesson: Ztschr. f. physiol. Chem. **15**:404, 1891.
12. Araki: Ztschr. f. physiol. chem. **19**:447, 1894.
13. Irisawa: Ztschr. f. physiol. chem. **17**:340, 1893.
14. Milroy: J. Physiol. **51**:272, 1897.
15. Penfield, W. G.: Am. J. Physiol. **48**:121 (Feb.) 1919.
16. McEllroy, W. S.: Acidosis in Shock, J. A. M. A. **70**:847 (March 23) 1918.
17. Guthrie: Am. J. Physiol. **45**:544, 1918.
18. Erlanger, J., and Gasser, H. S.: Am. J. Physiol. **50**:116 (June) 1919.
19. Gesell, R.: Am. J. Physiol. **47**:459 (Jan.) 1919.

of experimental shock, according to Macleod,[20] is associated with a demonstrable increase of lactic acid in the blood—an effect attributed by him to anoxemia because of depression of both the respiratory and the circulatory functions. All the conditions described above, which are associated with an increase of lactic acid or a reduced alkali reserve, are characterized by diminished blood volume, or diminished blood pressure, or decreased carrying power of the corpuscles, so that the delivery of oxygen to the tissues is reduced. It is well proved that in the absence of adequate oxygen supply the lactic acid which accompanies muscular contraction, for example, is not burned to carbon dioxid and water.[21] The liberation of such acid would produce the effects which have been observed—a demonstrable increase of lactates in the blood, and a diminution of sodium bicarbonate. It may be, as Wertheimer, Fabre and Clogne[22] have noted, that diacetic acid is present in some instances.

The other explanation for the reduced blood alkali attributes the change to relative increase of pulmonary ventilation. Henderson and Haggard[23] have reported that if they permit an animal to breathe to excess, as it naturally does during the development of shock from trauma of the abdominal viscera, failure of the circulation and death are induced. This is associated with a lowering of both the carbon dioxid content and the carbon dioxid capacity of the blood and also a lowering of the arterial pressure. In explanation of these results, Henderson and Haggard[24] have found that when animals are subjected to progressively decreasing oxygen percentages, the first effect is an abnormally large loss of carbon dioxid from the body due to excessive breathing and that thereafter alkali passes out of the blood to compensate for the alkalosis thus developed. In other words, when the carbonic acid of the blood is lowered, sodium bicarbonate also falls. A modification of this view has been suggested by Moore,[25] who assumes that as a consequence of shock there is a general lowering of metabolic activity to about one-third the normal rate. If then the lungs continue functioning at their usual rate, or even less, there will be removed from the blood an excess of carbon dioxid over that which is produced, and the blood will be altered in the alkaline direction.

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20. Macleod, J. J. R.: Am. J. Physiol. **55**:190 (March) 1921.

21. Fletcher and Hopkins: J. Physiol. **35**:298, 1907.

22. Wertheimer, Fabre and Clogne: Bull. et mém. Soc. de chir. **45**:9, 1919.

23. Henderson, Yandell, and Haggard, H. W.: J. Biol. Chem. **33**:371 (Feb.) 1918.

24. Henderson, Yandell, and Haggard, H. W.: J. Biol. Chem. **43**:3 (Aug.) 1920.

25. Moore, B.: Lancet, **2**:474 (Sept. 13) 1919.

Thereupon, the kidneys and tissue cells remove alkali from the circulation; and if the blood is examined for circulating sodium bicarbonate, a lower figure than the normal is obtained.

With reference to the argument in the foregoing explanations, we may admit at once that excessive breathing due to oxygen want may have the effect which Henderson has reported. Further, we may admit that in the presence of an excess of alkali, the tendency of the tissues, and of the kidneys, in case there is sufficient blood pressure to permit them to act effectively, would be to remove the excess from the blood stream. There is some question, however, whether the hyperpnea assumed by Henderson, or the continued normal breathing in the absence of adequate stimulation (i.e., the normal carbonic acid content of arterial blood), assumed by Moore, are actually present in cases of shock in human beings. Certainly the method of inducing excessive respiration in experimental shock which Henderson employed, that of positive overventilation of the lungs or vigorous manipulation of the diaphragm, does not represent the conditions attending the onset of

TABLE 2.—Relation of Carbon Dioxid Capacity to Respiration

No. of Cases	Carbon Dioxid Capacity	Average Respiratory Rate
17	40 to 49 (av. 44)	24
7	30 to 39 (av. 35)	28
6	20 to 29 (av. 24)	44

shock as seen in man. The classic descriptions of shock refer to respiration as being shallow and feeble, interrupted by occasional sighs. Such was the character of the breathing noted in numerous cases of shock at Béthune. The rate, as shown in Table 2, is likely to be much more rapid than normal; but since the breathing is shallow, the result is not likely to be an effective ventilation of the lungs.[26] In three cases of shock in man observed by Aub, the ventilation per minute ranged between 5.77 and 7.19 liters. In three other wounded men with normal blood pressures, the average figure was 8.2 with a range of from 6.81 to 9.59 liters per minute. It is unfortunate that it was impossible to obtain more evidence regarding the volume of ventilation in shock observed in human beings. If respiration is shallow, however, it seems probable that there would be no reduction or relatively slight reduction of the alveolar carbon dioxid, and a consequent lessening of the concentration of carbon dioxid in the blood. According to Henderson and Haggard,[27] morphin, by depressing respiration, tends to cause accumulation of carbonic acid in the blood, and therefore prevents the lowering of the

26. Edsall: Boston M. & S. J. **167**:647, 1912.

27. Henderson, Yandell, and Haggard, H. W.: J. Biol. Chem. **33**:344 (Feb.) 1918.

alkali reserve. In the cases of human shock, as observed in Béthune, morphin was given as a routine procedure shortly after the men were wounded. In Table 3 are presented figures showing the systolic and diastolic blood pressures, the carbon dioxid capacity and the morphin dosage in eleven typical cases. These figures demonstrate that prompt administration of morphin, even in doses of one-half grain (0.0324 gm.) may not prevent a reduction of the alkali reserve.

Besides doubt as to whether excessive respiration is present in human shock, there is further question whether it would have, if present, a causal relation to the onset of the shock state. Aub [28] found that the volume of respiration per minute, in experimental shock produced by muscle injury, increased in ten experiments 54 per cent. above the average for the controls. This was, however, before the onset of shock. When the condition of shock became established, the increase

TABLE 3.—Systolic and Diastolic Blood Pressures, the Carbon Dioxid Capacity and the Morphin Dosage in Eleven Typical Cases

Blood Pressure		Carbon Dioxid Capacity	Morphin Dosage, Grain
Systolic	Diastolic		
92	70	49	¼
79	56	30	½
64	40	21	½
76	46	41	¼
42	28	40	¼
72	48	38	½
80	58	43	¼
56	20	26	¼
92	62	47	¼
68	42	36	½
75	46	36	¼

was only 14 per cent. above the controls. One might assume that this indicated that the increased volume of respiration was causally related to the development of low blood pressure. Aub repeatedly observed, however, a rapid breathing with a large increase of the ventilation rate per minute under urethane anesthesia without the onset of shock. Furthermore, uniform artificial respiration may be given to an animal while passing into the state of shock, and under these circumstances no diminution of the carbon dioxid capacity of the plasma occurs until the blood pressure falls. Thus, the respiratory factor is not permitted to vary, and the excessive respiration, as postulated by Henderson, is not capable of producing the changes which he regards as the consequence of hyperpnea. Nevertheless, a low pressure develops, and as the pressure continues to fall, there is a reduction of the alkali reserve. In one such instance, the blood pressure fell in half an hour from 110 to 40 millimeters of mercury with a decline in carbon dioxid capacity of 12 per cent. by volume. In the later stages of this fall of

28. Aub, J. C.: Am. J. Physiol. **54**:388 (Dec.) 1920.

pressure, there might have been a lessening of the carbon dioxid content of the blood because of uniform respiration in the presence of diminished metabolism, but the drop of pressure could hardly be accounted for on the basis of hyperpnea. From all this evidence, it seems probable that the conditions Henderson established in his experiments do not account for the results observed in cases in human beings, and that the reduced alkali may be explained as a consequence of diminished volume-flow to the tissues.

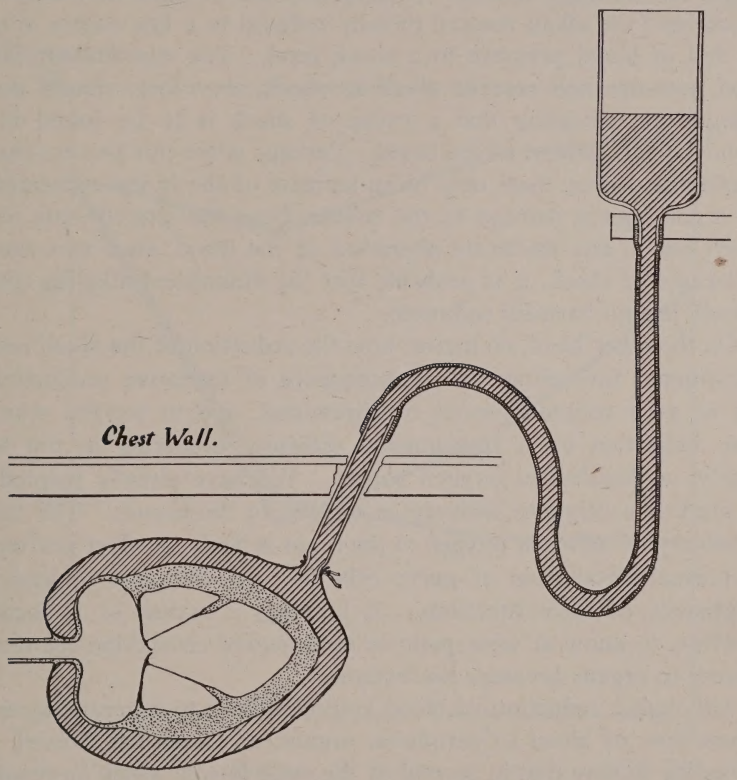

Fig. 1.—Arrangement for controlling the cardiac output and consequently the height of arterial pressure by means of increasing or decreasing intrapericardial pressure.

So far as Moore's contentions are concerned, there is no evidence that the metabolism in shock is reduced to any marked degree until there is a considerable fall of arterial pressure.[28] In other words, the low metabolism may reasonably be regarded as a consequence of the diminished oxygen supply. The reduction of the alkali reserve which has been observed to accompany a diminished oxygen supply may be satisfactorily explained, therefore, on that basis, rather than on the

28. Aub, J. C.: Am. J. Physiol. **54**:388 (Dec.) 1920.

assumption that with continued normal respiration and a diminished carbon dioxid production a primary alkalosis results, followed by escape of the excess alkali.

SIGNIFICANCE OF REDUCTION OF THE ALKALI RESERVE IN SHOCK

Experiments by Dale and Richards [29] and also by Gesell [30] have shown that a large amount of acid may be injected into the blood stream, and the alkali reserve thereby reduced to a low degree without any fall of blood pressure to a shock level. The concomitant fall of blood pressure and reserve alkali in shock, therefore, should not be regarded as indicating that a cause of shock is to be found in the lessened alkali content of the blood. Perhaps when this process reaches an extreme degree, there may be an increase of the H-ion concentration and a consequent damage to the tissues from the altered state of the blood; but in any moderate alteration of the blood, such as occurs in most cases of shock, it is probable that the diminished alkaline content in itself has no harmful influence.

On the other hand, no matter how the reduction of the alkali reserve is accounted for—either as a consequence of excessive production of acid or as a consequence of overbreathing, due to oxygen want—it is an indication of a fundamental difficulty occurring in the body, namely, an insufficient oxygen supply. We have already pointed out the need of continuous delivery of oxygen to the tissues. The failure of delivery of sufficient oxygen to the brain is likely to affect profoundly the normal metabolism of nerve cells in particular, and to lead to a disturbance of their functions. It becomes a matter of importance, therefore, to know at what point in an impaired circulation the oxygen delivery to organs becomes inadequate.

Although a reduction of blood volume affects to a great degree the volume-flow of blood to peripheral organs, as Gesell has proved, it is interesting to note that in several of the experiments which he reports [30] (Figs. 3 and 4), there is no marked reduction of the carbon dioxid content of arterial blood in a series of determinations, until the blood pressure falls to the neighborhood of 80 or 90 millimeters of mercury. Raymund [31] likewise has reported cases of experimental shock in which, after the initial reduction of the blood alkali attributable to etherization, a further reduction does not take place until the blood pressure falls below approximately 80 or 90 mm. of mercury. A similar relation is seen in several experiments performed by Henderson and Hag-

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29. Dale and Richards: Report of the Shock Committee, English Medical Research Committee, October, 1918, Series No. 25, p. 250.

30. Gesell, R.: Am. J. Physiol. **47**:481 (Jan.) 1919.

31. Raymund, B.: Am. J. Physiol. **53**:127, 130 (Aug.) 1920; Figures 2, 3 and 5*b*.

gard.[32] These results are in interesting agreement with both experimental and clinical studies which were carried on in France. This concordant testimony has practical importance. In the first place, it signifies that, though the reduced volume-flow is a highly disturbing condition, the final touch in rendering the circulation inefficient is ascribable to a slowing of the blood flow as the arterial head of pressure falls. In the second place, the observation has significance because of the ease of determining the head of arterial pressure by clinical

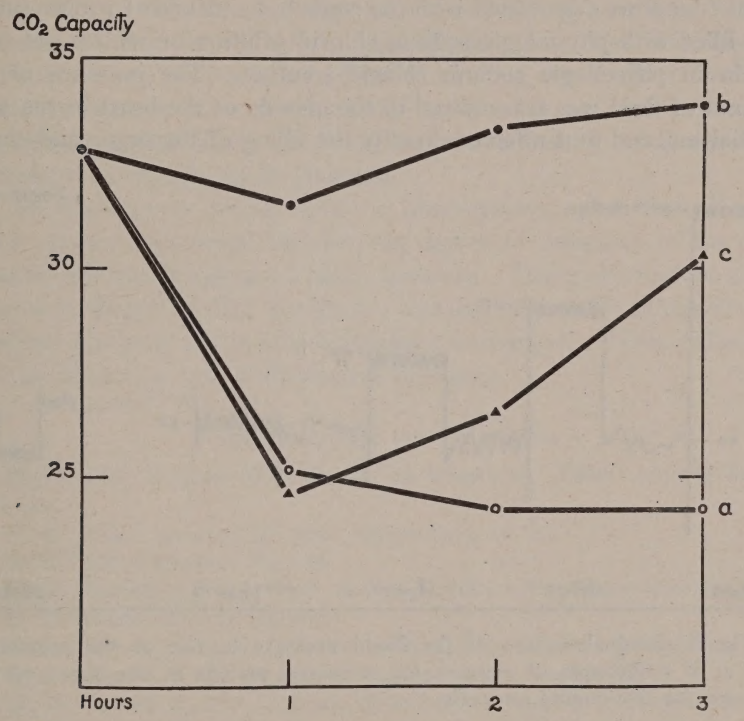

Fig. 2.—Changes in percentage by volume of carbon dioxid (the alkali reserve) of the blood plasma in cases in which the blood pressure was lowered to 60 millimeters of mercury for three hours; in *a* without other action, in *b* with previous injection of morphin, and in *c* with morphin injected after one hour of low pressure.

means and thus having a basis for a judgment as to whether the impairment of the circulation has reached a dangerous degree.

EXPERIMENTAL DETERMINATION OF THE CRITICAL LEVEL

In order to produce experimental conditions which would be as closely as possible analogous to those which analysis has shown to be

32. Henderson, Yandell, and Haggard, H. W.: J. Biol. Chem. **33**:365 (Feb.) 1918.

true for shock, and yet preserve the possibility of controlling accurately these conditions, we have made use of the arrangement illustrated in Figure 1, a modification of the method employed by Johansson and Tigerstedt [33] for recording the volume changes of the heart. Under artificial respiration, the thorax was opened between the ribs on one side at the level of the lower end of the sternum. A small slit was cut in the pericardium and a glass cannula tied in place. The thorax was then tightly closed and the animal allowed to breathe naturally. A small funnel was connected with the cannula by means of rubber tubing and filled with physiologic sodium chlorid solution or with 6 per cent. acacia in physiologic sodium chlorid solution. The pressure of the column of fluid was transmitted to the outside of the heart in the pericardial sac, and thus affected directly the filling of the organ and conse-

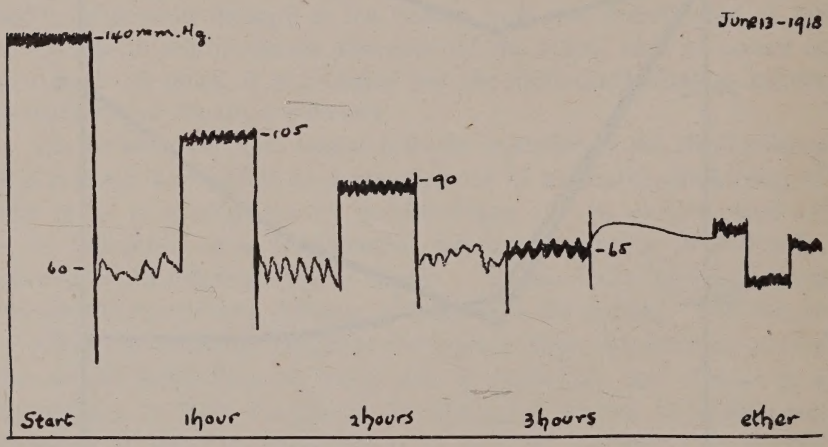

Fig. 3.—Gradual failure of the blood pressure to rise as the pressure is held at 60 millimeters of mercury for successive periods of one hour and then released for five-minute intervals.

quently its output. By raising or lowering the funnel, any desired arterial pressure could be produced and maintained. In a few experiments, the arterial pressure was regulated by compression of the heart by means of a clamp applied to the chest. This method gave similar results, but was inferior in that it interfered with the respiratory movements.

Most of the experiments were performed on cats; but in a few cases, rabbits or dogs were used. Ether was found to be a satisfactory anesthetic, for preliminary observations showed that under the conditions of our experiments it produced no effect on the alkali reserve. A cannula was placed in the pericardium to control the arterial pressure,

33. Johansson and Tigerstedt: Skandin. Arch. f. Physiol. **1**:344, 1889.

as described above. The blood pressure was recorded by a mercury manometer connected with one carotid; a second cannula was placed in the other carotid or in the femoral artery to obtain samples for the bicarbonate determinations. For each determination, about 3 c.c. of blood was taken in a graduated tube, centrifuged, and the alkali reserve of the plasma determined by the Van Slyke [7] method. A sample of blood was usually taken immediately before reducing the blood pressure and at intervals of an hour throughout the course of the experiment. As a rule, no difficulty was experienced in keeping a constant arterial pressure at any desired level. Sometimes, just after reducing the pressure, it was necessary to adjust the funnel repeatedly in order to hold the arterial pressure constant, but usually an equilibrium was reached in a short time. A few experiments had to be discarded on account of irregularities in pressure.

Throughout the whole series of observations, a satisfactorily constant relation was found between the degree of reduction of the alkali reserve and the lowering of blood pressure. The most marked reduction was found at low pressures, whereas above 80 millimeters of mercury the state of the blood remained unchanged. These differences can be shown by a few illustrative protocols.

PROTOCOLS OF EXPERIMENTS

EXPERIMENT 2.—May 10, 1918, cat, 3.6 kilograms. Ether; cannula in both carotids.

10:08: Blood pressure 178 mm.; temperature 36 C.

10:22: Blood pressure 160 mm.

10:23: Sample A, 3 c.c. blood; carbon dioxid reading 39 per cent. by volume.

10:24: Blood pressure 160 mm.

10:26: Arterial pressure reduced to 80 mm. by external pressure on chest.

11:27: Sample B, 3.2 c.c. blood; carbon dioxid reading 37.

12:24: Sample C, 3.0 c.c. blood; carbon dioxid reading ?; sample lost.

12:57: Sample D, 3.5 c.c. blood; carbon dioxid reading 38.

1:29: Pressure reduced to 60 mm.

2:28: Sample E, 2.7 c.c. blood; carbon dioxid reading 35.

3:01: Pressure removed from thorax; blood pressure gradually rose until 4:00 when it reached 112 millimeters of mercury.

4:01: Sample F, 4.5 c.c. blood; carbon dioxid reading 40.

EXPERIMENT 3.—May 11, 1918, cat, 2.9 kilograms. Ether; cannulas in both carotids; cannula in pericardium.

9:51: Blood pressure 124 mm.

9:53: Sample A, 5.0 c.c.; carbon dioxid reading 30.

10:00: Blood pressure fell to 80 mm.; kept at the level by intrapericardial pressure.

11:02: Sample B, 4.5 c.c.; carbon dioxid reading 31.

11:04: Pressure reduced to 60 mm.

12:03: Sample C, 4.0 c.c.; carbon dioxid reading 20.

12:08: Intrapericardial pressure removed; blood pressure rose to 116 millimeters of mercury.

12:31: Sample D, 4.0 c. c.; carbon dioxid reading 25.

12:32: Pressure reduced to 70 mm.

1:31: Sample E, 4.5 c. c.; carbon dioxid reading 23.

EXPERIMENT 16.—May 25, 1918; dog, 6.73 kilograms.

7:35: Morphin 0.056 gm.

8:45: Operation started; cannula in pericardium; carotid cannulas.

9:50: Sample A, 3.0 c. c.; carbon dioxid reading 33.

9:52: Blood pressure 120 mm.

10:12: Blood pressure 116 mm.

10:17: Blood pressure reduced to 60 mm. by intrapericardial pressure (gum-salt).

11:17: Sample B, 4.5 c. c.; carbon dioxid reading 22.

12:22: Sample C, 6.0 c. c.; carbon dioxid reading 20.

1:22: Sample D, 6.2 c. c.; carbon dioxid reading 19.

2:31: Sample E, carbon dioxid reading 20.

TABLE 4.—BLOOD PRESSURE REDUCED TO 80 MM.

Exp.	Animal	Orig. Blood Pressure	Carbon Dioxid Reading			
			Start	1 Hour	2 Hours	3 Hours
5/10	Cat	178	39	37	..	38
5/11	Cat	124	30	31	..	..
5/15	Dog	80	35	35	..	..
5/16	Dog	160	20	20	17	..
			Av. 31.0	30.8		

TABLE 5.—BLOOD PRESSURE REDUCED TO 70 MM.

Exp.	Animal	Orig. Blood Pressure	Alkaline Reserve				
			Start	1 Hour	2 Hours	3 Hours	4 Hours
5/11	Cat	116	25	23	..	..	..
5/13	Cat	170	33	31	25	..	..
5/27	Cat	142	30	27	32	34	35
6/14	Cat	168	34	29	29	32	33
			Av. 30.5	27.5			

The results for the series of experiments are summarized in Tables 4, 5, 6, 7 and 8. Cases in which the blood pressure was reduced to 80 millimeters of mercury are given in Table 4. In every case, the alkali reserve was unaffected by pressure at this level for an hour. Table 5 shows the effects at 70 mm. pressure. Here there is a slight reduction in the alkali reserve—an average fall of 3 per cent. by volume of carbon dioxid. In the two cases in which observations were continued for four hours, a recovery took place. This occurred in a certain number of cases, even at lower blood pressures. The phenomenon will be referred to again. The next two tables present the results for an arterial pressure reduced to 60 millimeters of mercury, Table 6 giving

figures for cases in which the low pressure was continued for only one hour, and Table 7 for cases of low pressure for three hours. With this pressure, it will be noted that there was a marked fall in the alkali reserve during the first hour, indicating that the circulation was no longer adequate to maintain normal oxidation in the body. During the second hour, the average of the results shows a slight further fall; but during the third hour, there is no further change. Table 8, giving

TABLE 6.—Blood Pressure Reduced to 60 Mm. for One Hour

Exp.	Animal	Orig. Blood Pressure	Alkaline Reserve		
			Start	1 Hour	2 Hours
5/10	Cat	178	38	35	..
5/11	Cat	124	31	20	..
5/24	Rabbit	...	27	18	..
6/ 5	Cat	...	37	20	..
7/15	Cat	136	30	19	18
7/16	Cat	114	26	19	..
			31.5	21.8	

TABLE 7.—Blood Pressure Reduced to 60 Mm. for Three Hours

Exp.	Animal	Orig. Blood Pressure	Alkaline Reserve				
			Start	1 Hour	2 Hours	3 Hours	4 Hours
5/ 9	Cat	130	39	36	32	32	..
5/25	Dog	120	33	22	20	19	20
5/29	Cat	128	35	32	33	33	..
6/13	Cat	140	31	14	18	19	..
7/13	Cat	118	37	29	29	27	29
7/20	Cat	109	33	30	25	27	..
			34.7	27.1	26.1	26.1	

TABLE 8.—Blood Pressure Reduced to 50 Mm.

Exp.	Animal	Orig. Blood Pressure	Alkaline Reserve			
			Start	1 Hour	2 Hours	3 Hours
5/28	Cat	174	27	14	11	..
6/ 5	Cat	...	37	19	..	..
7/18	Cat	86	28	20	23	21
7/23	Cat	96	41	29	..	17
			Av. 33.2	20.5		

effects of the reduction of the blood pressure to 50 millimeters of mercury, reveals a still greater fall in the alkali reserve; at the end of one hour, the percentage by volume of carbon dioxid reached the low figure of 20.5.

An examination of the data presented in the accompanying tables shows a normal bicarbonate reserve in the cat of from 39 to 25, the average being about 32. This is a much lower figure than that found in normal human plasma, where a reading below 50 is generally considered to be pathologic. The most rapid fall in the alkali reserve occurs

during the first hour of reduced pressure, after which it soon reaches a stationary low level. In a few cases, there is an actual recovery after several hours. It may be that by lessened cellular activity the organism adapts itself to the condition of low pressure; and then, because the oxygen requirement becomes less, the acids may be reduced by oxidation. There is another possibility which might be considered. Clearly, if the pressure is artificially kept constant throughout an experiment, it is possible that after several hours a peripheral dilatation takes place, due to lessened vasomotor tone or to direct effect of metabolites, and thus with a constant pressure the blood flow would be increased.

The alkali reduction produced by an inadequate circulation is not permanent, but rapidly disappears when the blood pressure is allowed to return to normal, as is shown above in the first two protocols. In a number of other instances, the blood pressure was raised by injection of gum-salt solution, and the alkali reserve was restored.

TABLE 9.—Results Obtained in Four Animals in Which Pressure was Reduced to 80 or 90 Mm. After Removing 20 Per Cent. of Blood

	Blood Pressure		Alkali Reserve		
Exp.	Orig.	Final	Start	1 Hour	2 Hours
5/14	175	80	31	26	23
5/21	150	80	20	16	..
5/23	100	90	37	35	35
6/16	150	90	33	33	..

Many cases of low blood pressure in wounded men were complicated by hemorrhage. The question arose as to whether loss of blood modified the critical level of the blood pressure. This was somewhat difficult to determine experimentally because in many animals the combination of an operation and the loss of blood reduces the blood pressure below the desired level. Satisfactory results were obtained in four animals (Table 9). In each case, they were bled 20 per cent. of their calculated blood volume before reducing the pressure. The two cases with arterial pressure reduced to 80 millimeters of mercury showed marked indications of an inadequate circulation, while those with a reduction to only 90 mm. showed less effect. It seems probable, therefore, that when hemorrhage complicates a low blood pressure the critical level is higher than when no loss of blood has occurred.

From these experimental results we conclude that the *critical level,* that is, the level at which the blood pressure is no longer capable of maintaining an adequate volume-flow to the tissues, and thus serving the normal oxidations of the body, is *approximately* 80 millimeters of mercury. Above 80 mm. reduction of the alkali reserve is not likely to appear; but as the pressure falls below this, a reduction will probably occur, which is more marked and develops the more rapidly the lower

the pressure. If there has been a loss of blood, the circulation becomes inadequate before the pressure falls to 80 millimeters of mercury, i.e., the critical level is raised. In this connection, the observations of Markwalder and Starling[34] are of interest. They found experimentally that cardiac contraction begins to weaken when the arterial pressure falls below 90 millimeters of mercury. Gruber[35] noted a marked decrease in the height of contraction of muscle which was being uniformly stimulated when he reduced the blood pressure to 90 millimeters of mercury. Above this level, however, changes in pressure produced practically no effect on muscular contraction. The results reported by Gesell, by Raymund and by Henderson and Haggard, mentioned above, likewise point to a pressure of 80 or 90 millimeters of mercury as being necessary for a sufficient blood flow.

Aub has studied the decrease of the metabolic rate in shock. In eight cases of severe shock, the average decrease was 33 per cent.[28] It was a matter of interest to learn whether the fall of metabolism was related in any way to the critical level of arterial blood pressure, as indicated by the appearance of acidosis. Aub found, indeed, that as a rule the critical level for metabolism was associated with a blood pressure in the neighborhood of 75 or 80 millimeters of mercury. At that level, the metabolism might be within the normal rate of variation; but usually when this was the case, the blood pressure had been remaining stationary or was rising. In other instances, he noted that when the blood pressure was at this level, or occasionally higher, the metabolism might be considerably reduced; but when this was the case, the blood pressure was in the process of falling. With a blood pressure below 75 millimeters of mercury the metabolism was invariably reduced beyond the common normal variations. These observations are confirmatory of the evidence already adduced in placing the threshold of adequacy of arterial pressure at approximately 75 or 80 millimeters of mercury.

THE EFFECT OF MORPHIN

As shown in Table 7, reduction of the blood pressure to 60 millimeters of mercury for three hours causes a marked and lasting reduction of the alkali of the blood plasma. Experiments performed by one of us (M.C.) at Dijon proved that morphin can modify this effect in a striking manner. A comparison of the average figures in Tables 10 and 11 with those in Table 7 is given graphically in Figure 2. The curves of each condition have been shifted so that they have a common initial point at the average of the first readings (32.8). Figure 2 *a* represents the results detailed in Table 7—a fall and continued low level of the

34. Markwalder and Starling: J. Physiol. **47**:279, 1913.
35. Gruber: Am. J. Physiol. **32**:227, 1913.

blood alkali when the blood pressure is held down to 60 millimeters of mercury. Figure 2 *b* represents Table 11, and Figure 2 *c* Table 10. In the former case, morphin sulphate (20 mg. per kilogram) was given subcutaneously just before the pressure was lowered; the alkali reserve was not reduced. In the latter case, it was given after the pressure had been kept at 60 mm. for one hour; the alkali reserve, which had fallen as in *a*, began to rise, and after two hours was largely restored.

TABLE 10.—Effects of Morphin Given One Hour After Reduction of Blood Pressure to 60 Millimeters of Mercury

Exp.	Animal	Orig. Blood Pressure	Alkaline Reserve				
			Start	1 Hour	2 Hours	3 Hours	4 Hours
6/ 7	Dog	138	24	15	11	12	18
6/ 8	Dog	128	23	16	20	22	23
6/10	Cat	150	35	21	27	29	34
6/17	Cat	120	35	35	37	42	..
6/18*	Cat	118	30	20	21	31	..
6/19*	Cat	150	32	23	23	28	..
6/20	Cat	156	36	21	23	22	22
6/24	Cat	120	26	24	29	35	36
			Av. 30.1	21.9	23.9	27.6	

TABLE 11.—Effects of Morphin Given Just Before Reducing Blood Pressure to 60 Millimeters of Mercury

Exp.	Animal	Orig. Blood Pressure	Alkaline Reserve				
			Start	1 Hour	2 Hours	3 Hours	4 Hours
6/26	Cat	100	32	34	39	37	35
6/27	Cat	134	35	32	36	37	39
6/29	Cat	142	29	27	27	31	33
7/ 8	Cat	114	41	33	35	34	..
10/27*	Cat	128	30	34	33	32	..
10/29*	Cat	120	34	33	34	37	35
			Av. 33.5	32.2	34.0	34.7	

The explanation of this conserving influence of morphin is still obscure. Henderson and Haggard [27] have reported that when, by means of morphin, respiration is depressed and the alveolar carbon dioxid is raised, the alkali reserve of the blood also rises; and they suggest that this rise is due to a passage of alkali from the tissues into the blood to compensate for the increase in carbonic acid. The reactions represented in Figure 2 *b* and *c*, however, occur in animals in which the breathing is kept mechanically regular by artificial respiration. In Table 10, the experiments of June 18 and 19, and in Table 11, the experiments of October 27 and 29 (marked by asterisks) were of this character. They do not differ in nature from the other experiments in the series in which the respiratory mechanism of the animal was allowed to function. It seems, therefore, that slowing of the respiration is not solely responsible for the preservation of the normal alkali reserve.

Possibly morphin, by reducing the activity of tissues, lessens their demand for oxygen and thus compensates for the smaller supply of oxygen in the sluggish blood flow. Further experiments are needed, however, before this suggestion should be accepted.

CLINICAL EVIDENCE FOR A CRITICAL LEVEL

After obtaining the foregoing experimental indications of a critical level, we went over the Béthune records of low blood pressure in cases of shock and hemorrhage in which determinations of the alkali reserve had been made simultaneously. These records were then tabulated on the basis of systolic blood pressure. The figures are given in Table 12. As the table shows, the alkali reserve rarely falls below

TABLE 12.—CRITICAL LEVEL OF BLOOD PRESSURE IN HUMAN CASES AS SHOWN BY THE ALKALI RESERVE (CARBON DIOXID CAPACITY)

Systolic Blood Pressure	Average Carbon Dioxid Capacity Percentage by Volume	Variation	No. of Cases
96–102	48	40–56	5
90– 92	49	41–58	7
82– 86	49	43–52	5
72– 78	43	30–49	10
62– 68	36	21–42	11
52– 59	24	20–27	5

the normal (approximately 50 per cent. by volume) until the systolic pressure lies below 80 millimeters of mercury. Furthermore, the greater the reduction of blood pressure below this critical level, the greater is the reduction of the carbon dioxid capacity or the alkali reserve. The significance of these observations will become more manifest as we consider how the reduced pressure is related to the damage suffered by sensitive structures when insufficiently supplied with oxygen.

VARYING SENSITIVENESS OF TISSUES TO WANT OF OXYGEN

In an extensive series of studies, Pike, Guthrie, and Stewart have examined the capacity of different tissues of the body to function after having been totally deprived of their blood supply for varying periods. In general, it may be stated that muscles and glands reveal a remarkable endurance of anemia.[36] The muscles will withstand this injurious condition much longer than the nervous system, for example. The same may be said of glandular structures.

The most sensitive cells in the body are found in the brain; but a remarkable gradation of resistance to anemia is found in different neurons. Most sensitive of all are cells of the cerebellum and cerebrum.

36. Pike, Guthrie and Stewart: Am. J. Physiol. **22**:51, 1908.

Mayer,[37] Batelli,[38] and also Stewart, Guthrie, Burns and Pike[39] have offered concordant evidence that after fifteen minutes of anemia, restoration of cerebral function is no longer constant. Gomez and Pike,[40] on examining the effects in detail, observed that the small pyramidal cells of the cortex are especially sensitive—eight minutes of anemia killed many of them—and that the Purkinje cells were next in order—thirteen minutes producing chromatolysis in them.

The cells of the medulla are more resistant. Gomez and Pike found that anemia for from eight to thirteen minutes produces in them only slight lesions or no changes at all, and that anemia should last for twenty to thirty minutes in order to produce alterations incompatible with complete recovery. The cells of the spinal cord apparently withstand a lack of blood flow for a somewhat longer period than those of the bulb; different observers have reported paralysis or recovery after shutting off the blood supply from forty-five to sixty minutes.[41] The outlying ganglions of the sympathetic chain, according to Schröder,[42] are even less delicate, for they can be completely deprived of blood supply for an hour and will then function if supplied with blood. Cannon and Burket[41] showed that the nerve cells of the myenteric plexus will endure anemia for as long as three hours without showing either loss of function, or change or disappearance of structure. From this evidence, it is clear that in the nervous system there is a hierarchy of cells with varying ability to meet the circumstances of insufficient oxygen supply.

In shock, of course, there is not a total absence of oxygen delivery to the tissues, as in the experiments reported in the foregoing paragraph. On the other hand, the indications are definite that even with the blood flowing, conduction in the nervous system may be completely checked when the oxygen supply becomes insufficient. In some experiments performed by E. L. Porter,[43] on variations in the irritability of a reflex arc under asphyxial conditions, it was discovered that when the oxygen supply is diminshed and accumulation of carbon dioxid in the blood is prevented, the reflex abruptly disappears when the oxygen content of the arterial blood is reduced on the average to 4.5 per cent. by volume. Lack of oxygen proved to be much more important than accumulation of carbon dioxid in abolishing the capacity to transmit nerve impulses.[44]

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37. Mayer: Centralbl. f. d. med. Wissensch. **16**:579, 1878.
38. Batelli: J. de physiol. et de path. gén. **2**:456, 1900.
39. Stewart, Guthrie, Burns and Pike: J. Exper. M. **8**:316, 1906.
40. Gomez and Pike: J. Exper. M. **11**:262, 1909.
41. Cannon and Burket: Am. J. Physiol. **32**:348, 1913.
42. Schröder: Arch. f. d. ges. Physiol. **116**:603, 1907.
43. Porter, E. L.: Am. J. Physiol. **31**:244, 1913.
44. Porter, E. L.: Reference 43, p. 231.

EVIDENCE OF DAMAGE TO THE CENTRAL NERVOUS SYSTEM FROM LOW BLOOD PRESSURE

The testimony that insufficient blood supply injures the elements of the central nervous system is both morphologic and functional.

Morphologic changes as a consequence of diminished blood flow have been reported by Dolley,[45] who found that after repeated hemorrhage the Purkinje cells of the cerebellum underwent a sequence of alterations exactly identical with those observed in shocked animals. Mott[46] has reported studies of the cell changes in cases of shock in which some hours before death there was low blood pressure, and has found that there is general chromatolysis, a change which he attributes to the prolonged anoxemia. Besides the chromatolysis, Mott noted that many of the cells of the medulla and also some of the Purkinje cells show a tendency to profuse purple staining when a double stain, such as a basic blue and eosin dye, is used. This alteration in the staining reaction denotes a biochemical change, possibly different in character from that associated with the diffusion of the Nissl substance.

The functional evidence of injury to the nervous system from low blood pressure has come mainly from examination of disturbances in vascular reflexes during the development of shock. W. T. Porter and his collaborators proved that after a prolonged low blood pressure in shocked animals stimulation of afferent nerves could cause either a rise or fall of blood pressure.[47] They concluded, therefore, that even in extreme shock the vasomotor center is still active. It was not, however, until perfusion experiments were performed on peripheral vessels still connected with the vasomotor center that direct proof was obtained showing whether the center was overactive or underactive. Such perfusion experiments conducted by Erlanger, Gesell and Gasser,[48] and more recently by Cattell,[49] have demonstrated that although in the early stages of shock, whether due to abdominal injury or to crushing of muscle, the vasomotor tone is increased. In the later stages, there is practically invariably diminished tone and lessened peripheral resistance. The tendency of the vasomotor center, when the blood pressure becomes low, is to compensate by increased activity. The failure of the center to respond thus to the stimulus of a low pressure in the late stages of shock must be regarded, therefore, as signifying that the center has become injured to such a degree that it is incapable of responding.

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45. Dolley: J. M. Research, **16**:96, 1909.

46. Mott: Report of the Shock Committee, English Medical Research Committee, March, 1919, Series No. 26, p. 46.

47. Porter, W. T.: Am. J. Physiol. **20**:399, 1907; ibid. **20**:500, 1908.

48. Erlanger, J.; Gesell, R., and Gasser, H. S.: Am. J. Physiol. **49**:151 (July) 1919.

49. Cattell, McKeen, quoted by Cannon, W. B.: Arch. Surg. **4**:1 (Jan.) 1922.

Bayliss [50] has pointed out that the vasomotor center is not the only bulbar center that suffers from low blood pressure and the consequent sluggish blood flow. He noted that when the average blood pressure remained below 58 millimeters of mercury in cats, not only were vasomotor reflexes abolished but the rate of respiration fell to 6 or less per minute. Various other experiments showed that when the blood pressure was less than 70 millimeters of mercury from one and a half to two hours, more or less, a paralysis of the bulbar centers would occur. The respiratory center in the cat appears to suffer before the vasomotor center, though it may continue to discharge at the slow and ineffective rate of 3 or 4 per minute when the vasomotor center has lost its excitability. Bayliss suggests that different animals probably behave differently as regards the order in which their vital centers fail and that in man the vasomotor center may begin to lose its functional stability before the respiratory center.

In order to secure evidence as to the progressive nature of the damage done to the nervous control of the circulation in consequence of an insufficient blood flow, we have made observations on the effects of reducing the blood pressure to 60 millimeters of mercury for varying times by the method of intrapericardial compression of the heart (see p. 314). When the pressure had been thus reduced to that level it was held there for an hour. The compression of the heart was then released by lowering the fluid column. Usually, when this is done, the blood pressure will be restored completely or nearly completely to its normal level (Fig. 3). If then the pressure is again lowered to 60 mm. and held there for an hour, it does not rise so high; and when held to this low level for another hour, it may not rise at all.

It might be supposed that the failure of the pressure to rise after being held persistently low for three hours would be due to a loss of blood volume by escape of plasma into the tissues through more permeable capillary walls. Observations with the hematocrit in these cases, however, suggest that this was not an important factor. In Table 13 are the average hematocrit readings when the pressure was reduced to different levels and held there for periods of one, two and three hours. As the figures clearly show, the percentage of corpuscles gradually fell, indicating that there was a dilution, rather than a concentration, of the arterial blood.

The explanation which appears most reasonable to account for the failure of the pressure to rise after persistence at the low level is that the nervous agencies which control the circulation have suffered damage —a damage due to inadequacy of the circulation itself. The reason-

50. Bayliss, W. M.: Intravenous Injections in Wound Shock, London, New York, Longmans, Green & Co., 1918, p. 11.

ableness of the conclusion is supported by observations on relaxation of vascular tone in late shock,[49] and by tests of the responsiveness of the vasomotor center to stimulation by asphyxia. At an early stage in shock, there may be an asphyxial rise of pressure, and later, though the heart still beats and respiration is still active, the asphyxial rise does not occur, i. e., the vasomotor cells are no longer excited by the blood

TABLE 13.—Hematocrit Readings After Reduction of the Blood Pressure by Intrapericardial Compression

No .of Cases	Pressure Reduced to Mm. Hg	Average Hematocrit Readings (Percentage of Corpuscles)			
		Start	1 Hour	2 Hours	3 Hours
4	70	47	46	46	47
12	60	40	37	31	27
4	50	38.5	34.5	26	26

changes. LaCroix[51] has noted that in cases of shock after severe wounds there may be total immobility of the pupil, no matter how intense the light. This failure of the pupillary reaction points to a block of the nerve impulses along the reflex path involved in the reaction and is further indication of injury to the nervous elements.

IMPORTANCE OF THE TIME FACTOR IN THE DEVELOPMENT OF SHOCK

Experiments cited above have definitely proved that with an acute lack of oxygen nerve cells abruptly cease to function. The loss of consciousness when one faints is a common example of the close dependence of nervous elements on continuous oxygen supply. The experimental and clinical observations on the effects of prolonged low pressure point to the fact that these sensitive cells may be gradually harmed, if, instead of acute anemia, there is prolonged partial anemia.

The gradually damaging effect of persistent low blood pressure is of the utmost importance both in understanding and in treating shock. When the vasomotor center has lost its capacity to maintain vascular tone, there is no sort of remedial agent which can be applied to bring the blood flow back to its normal condition. If, in an animal, the medulla is destroyed, the blood pressure falls to approximately 40 millimeters of mercury and there remains. Intravenous injections of blood or other fluid will raise the pressure for only a few moments. An incredible amount of fluid may thus be introduced into the vessels without any lasting rise of pressure. When a man has been in a state of shock for a long time, so that the vasomotor center fails to hold the blood vessels in a state of moderate contraction, he reacts much as the experimental animal does when the bulbar centers are destroyed.

51. La Croix: Bull. et mém. Soc. de Chir. de Paris, **44**:906, 1918.

Transfusion leads to no permanent gain—the beneficial effect is fleeting. When that stage has been reached, the secondary harm from insufficient oxygen has been too great to permit resuscitation.

The foregoing considerations emphasize the prime importance of early treatment of the low blood pressure of shock. As Pike and Coombs [52] have stated, injured nerve cells require a better blood supply for their restoration than uninjured nerve cells do for their maintenance. Thus, though the tissues may not suffer until blood pressure has fallen below a critical level of approximately 80 millimeters of mercury, it is desirable, when the pressure has fallen below this level and has shown no evidence of rising, that it be raised to the normal level of 120 millimeters of mercury, if possible, in order to provide the most favorable conditions for repair of the damage which has been done.

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52. Pike, F. H., and Coombs, H. C.: Relation of Low Blood Pressure to a Fatal Termination in Traumatic Shock, J. A. M. A. **68**:1892 (June 23) 1917.